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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
OGIHARA,N	
ART UNIT	**PAPER NUMBER**
1631	9

DATE MAILED: 08/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/244,984	Applicant(s) BLACK ET AL.	
	Examiner Nancy Ogihara	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-62 is/are pending in the application.

4a) Of the above claim(s) 1-39 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 40-62 is/are rejected.

7)☒ Claim(s) 43 is/are objected to.

8)☒ Claims 1-62 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claims 1-62 are pending in the instant application. Applicant's election with traverse of Group V, claims 40-62, in the paper filed 7/11/00 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-39 are withdrawn from further consideration as being drawn to a non-elected invention.

Priority

This application claims priority to provisional application 60/073,709 filed 02/04/98, provisional application 60/117,476 filed 01/27/99, and provisional application 60/135,499 filed 03/30/98 under 35 U.S.C. 119(e).

Specifications

The disclosure is objected to because of the following informalities: In the brief description of drawings, it is noted that the description for Figures 2 describes colors which are not present in the figure. Appropriate correction is required.

Claim Objections

Claim 43 is objected to for referencing a table in the recitation of the claims. The MPEP 2173.05(s) states:

> Where possible, claims are to be complete in themselves. Incorporation by reference to a specific figure or table "is permitted only in exceptional circumstances where there is no practical way to define the invention in words and where it is more concise to incorporate by reference than duplicating a drawing or table into the claim. Incorporation by reference is a necessity doctrine, not for applicant's convenience." Ex parte Fressola, 27 USPQ2d 1608, 1609 (Bd. Pat. App. & Inter. 1993) (citations omitted).

Claim Rejections - 35 USC § 112

Claims 40-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for designing the TNF-α converting enzyme (TACE) inhibitor compound N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-

alanine,2(amino)ethyl amide, does not reasonably provide enablement for designing other associating compounds, and fails to enable the scope of the claims.

The claims are directed to a method for identifying a compound that associates with TACE comprising the step of designing and computationally modeling onto the X-ray structure of TACE a compound that interacts with the catalytic domain. The specification discloses only the co-crystallization and presumable modeling (i.e. design) of the compound N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide (see Figure 2A and Example 2 page 36) to the TACE protein. No other compounds are disclosed in the specification, either hydroxamate-based or other classes of compounds. Binding of one hydroxamate-based compound such as N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide to TACE does not fairly suggest that TACE will similarly bind to other compounds encompassed by the broad genus of hydroxamate-based compounds, or even other compounds outside of the genus, because of the broad heterogeneity (in size, geometric constraints, and ionic and hydrophobic properties) of possible chemical groups. In addition, the specification fails to sufficiently teach of the association of binding compounds that are not inhibitors. Non-inhibitor binding compounds such as activators or co-factors would not be expected to interact in the same fashion as the disclosed inhibitor of the co-crystal structure, as non-inhibitors have differing effects on the function of TACE, and can be expected to have differing modes of binding, and therefore have differing atomic interactions that are not predicted solely by the single structure of N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide bound to TACE. As taught by Rutenber et al, simplified models do not predict the binding of a ligand because 1) molecular water and counterions were not considered, 2) only steric interactions were considered, 3) a fixed structure of a ligand was used, and 4) a fixed conformation of the protein was used (J. Biological Chem., Vol. 268(21), pp. 15343-15346, 1993).

Identifying binding compounds by designing and modeling on the disclosed co-crystal structure is unpredictable and would require undue experimentation as there is no reasonable expectation of successfully identifying an associating compound based solely on the single disclosed co-crystal structure. Therefore, the specification does not enable any person skilled in the art to which

it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with claims.

Claims 40-62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for designing an associating compound based on the co-crystal structure of inhibitor-bound truncated TACE, which contains residues 215-477, the mutations S266A and N452Q, and the addition of a His-tag sequence to the C-terminus, does not reasonably provide enablement for designing other associating compounds to native TACE, and fails to enable the scope of the claims.

The claims are directed to a method for identifying a compound that associates with TACE comprising the step of designing and computationally modeling onto the X-ray structure of TACE a compound that interacts with the catalytic domain. The specification discloses only the co-crystallization and modeling (i.e. design) of N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide (see Figure 2A and Example 2 page 36) to a modified TACE protein where the modified TACE protein comprises a truncated protein containing residues 215 (or 219) to 477, the mutation of serine 266 to alanine, the mutation of asparagine 452 to glutamine, and the addition of Gly-Ser-$(His)_6$ to the C-terminus (see Example 1, page 34 lines 5-9). It should be noted that the PDB coordinates as shown in Table 1 on pages 40-77 contain only residues 219-474 of TACE. The disclosed co-crystal structure is not necessarily representative of the native protein structure to which the designed associating compounds will be targeting. The claimed methods do not take into account the N-terminal 214 amino acid residues of TACE which have an unspecified structure/function role on the binding of an associating compound and the subsequent mechanism of modulation of the protein. For example, it is not certain from the specification whether the N-terminal 214 residues will sterically block and prevent binding of N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide to full-length TACE. Furthermore, it is not certain what effects the point mutations and the His-tag sequence at the C-terminus sites have on folding, function, and ability of the full-length protein to bind compounds. Furthermore still, the specification does not take into account the native unliganded form of the protein, or the possible domain movements that may occur upon binding of an associating compound (i.e. induced fit type movements).

Because of the above mentioned uncertainties, identifying binding compounds by designing and modeling based on the disclosed co-crystal structure of truncated/mutated TACE is unpredictable and would require undue experimentation as the method does not take into account the structural differences between the disclosed structure and the native protein.

Claims 48-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for designing the TACE inhibitor compound N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide based on its co-crystal structure, does not reasonably provide enablement for designing other inhibitor compounds co-crystallized with TACE, and fails to enable the scope of the claims.

Applicant failed to disclose co-crystals comprising TACE and an inhibitor compound other than N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide. Although applicant discloses the structure solution and modeling of TACE, with the above mentioned inhibitor compound, applicant has not shown that other compounds will also co-crystallize in a similar fashion, given the (often times) difficulty and empirical nature of crystallizing proteins (see IDS document: Gilliland et al., Current Opinion in Structural Biology, vol. 6, 595-603, 1996; Introduction). Because of the unpredictability of protein crystallization, crystallizing one peptide in a binary complex cannot predict complex formation with other compounds. In particular, co-crystallization of TACE to compound N-{D,L-2-(hydroxyaminocarbonyl)methyl-4-methylpentanoyl}-L-3-amino-2-dimethylbutanoyl-L-alanine,2(amino)ethyl amide does not necessarily predict that TACE will co-crystallized with compounds encompassed by the broad genus of hydroxamate-based compounds, or even other compounds outside of the genus because of the broad heterogeneity (in size, ionic, and hydrophobic properties) of possible chemical groups. Since the specification provides no disclosure of additional co-crystals comprising TACE and associating compounds , the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with claims.

Claims 40-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 40 is vague and indefinite in the recitation of the abbreviated term "TNF-α." The full name of TNF-α should be completely spelled out at its first appearance and not abbreviated. Appropriate correction is required.

Claim 40 recites the limitation "catalytic domain." The metes and bounds of the claim are unclear since applicant fails to point out what residues of the polypeptide sequence are encompassed by the term "catalytic domain." The specification and claims do not indicate what residues constitute the beginning and end of the recited domain.

Claim 40 recites the limitation "said polypeptide." There is insufficient antecedent basis for this limitation in the claim as the term "polypeptide" is not recited previously in the claim. Does applicant intend to recite "compound"?

In claim 40, applicant recites the phrase "diffraction coordinates of a TNF-α converting enzyme polypeptide crystal." The term "diffraction coordinates" suggests the locations of intensity peaks in reciprocal space of a diffraction pattern, and not the atomic coordinates of a protein model obtained from X-ray diffraction experiments.

Claim 40 is vague and indefinite in the recitation of the abbreviated term "TNF-α." The full name of TNF-α should be completely spelled out at its first appearance and not abbreviated. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40-42 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Gomis-Ruth et al (IDS document: Protein Science, vol. 7, pp. 283-292, February 1998).

Gomis-Ruth et al disclose a method for identifying a compound that associates with TNF-α converting enzyme (TACE) using a theoretical crystal structure of the TACE polypeptide based on a

structural sequence alignment to the X-ray crystal structure of Adamalysin II (see Figure 7 and page 288). The inhibitors Pol 647 and Pol 656 were synthesized (see Materials and methods) and modeled onto the TACE structure where their interactions (i.e. associate capabilities) were determined. As with Adamalysin II, the inhibitor Pol 656 occupies the S1' pocket of TACE (see Figure 7 and page 285 under Inhibitor binding). It should be noted that the claim wording does not have a limitation preventing the theoretical modeling of a crystal structure of TACE based on a structural sequence alignment to a homologous protein such as Adamalysin II, or that it is limited to a physical crystal from which experimental X-ray diffraction data was collected to obtain structural coordinates. A theoretical TACE crystal model derived from Adamalysin II comprises X-ray diffraction coordinates, which necessarily take into account crystal packing interactions of the parent crystal model (i.e. Adamalysin II) from which the model is based. Therefore, the modeling of inhibitors onto the diffraction coordinates of a TACE theoretical polypeptide crystal by Gomis-Ruth et al meet the limitations of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 40-42 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cirilli et al (IDS document: FEBS Letters, vol. 418, pp. 319-322, 1997), in view of Gomis-Ruth et al (IDS document: Protein Science, vol. 7, pp. 283-292, February 1998).

Cirilli et al disclose a theoretical crystal model of TNF-α converting enzyme (TACE) based on a structural sequence alignment to the X-ray crystal structure of Adamalysin II (see Table 2 and page 321 last full paragraph). Cirilli et al disclose the structure of the inhibitor-bound S1' binding pocket (within the catalytic domain) of Adamalysin II (see Figures 3 and 4) and make comparisons to the TACE S1' binding pocket. Cirilli et al disclose the potential advantages of finding TACE inhibitors to reduce immunological damage of TNF-alpha (see page 319, right column).

Cirilli et al do not teach of a method of identifying a compound that associates with the TACE catalytic domain comprised of designing an associating compound, synthesizing the compound, and determining its interaction with TACE.

The teachings of Gomis-Ruth are set forth above.

Given that 1) Cirilli et al have taught of a theoretical crystal model of the TACE catalytic domain, and 2) that Gomis-Ruth et al have taught of identifying and modeling inhibitors Pol 647 and Pol 656 into a structural model of the S1' binding pocket of TACE, synthesizing the inhibitors, and determining binding interactions, it would have prima facie obvious to one of ordinary skill in the art at the time the invention was made to model, synthesize, and determine binding interactions between Pol 647 and Pol 656 and the theoretical TACE crystal structure of Cirilli et al. One of ordinary skill in the art would have been motivated to combine the model of Cirilli et al with the modeling methods of Gomis-Ruth et al in view of the potential advantages of identifying potential inhibitors of TACE for therapeutic use in reducing damaging effects of TNF-alpha.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy Ogihara whose telephone number is (703) 308-9363. The examiner can be reached Monday-Friday from 8:30-6:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Michael Woodward can be reached at (703) 308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center receptionist, whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1631 by facsimile transmission. Papers should be faxed to Group 1631 via the PTO Fax Center located in Crystal Park I. The faxing of such papers must conform with the notice published in the Official 1Gazette 1096 OG 30 (November 15, 1989). The CMI Fax Center number is (703) 308-4242.

Nancy Ogihara
July 25, 2000

ARDIN H. MARSCHEL
PRIMARY EXAMINER